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USAN 11/501,464  
For IDS filed 11/10/06



(19) Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number: 0 380 063 B1

(12)

## EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification :  
21.07.93 Bulletin 93/29

(51) Int. Cl.<sup>5</sup> : C07D 295/135, C07D 405/08,  
A61K 31/40

(21) Application number : 90101339.1

(22) Date of filing : 23.01.90

(54) 1,2-cyclohexylaminoaryl amides useful as analgesic agents.

(30) Priority : 24.01.89 US 301219

(43) Date of publication of application :  
01.08.90 Bulletin 90/31

(45) Publication of the grant of the patent :  
21.07.93 Bulletin 93/29

(84) Designated Contracting States :  
AT BE CH DE DK ES FR GB IT LI LU NL SE

(56) References cited :  
EP-A- 0 147 085  
EP-A- 0 167 253  
DE-A- 2 749 950  
DE-A- 3 241 933

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EP 0 380 063 B1

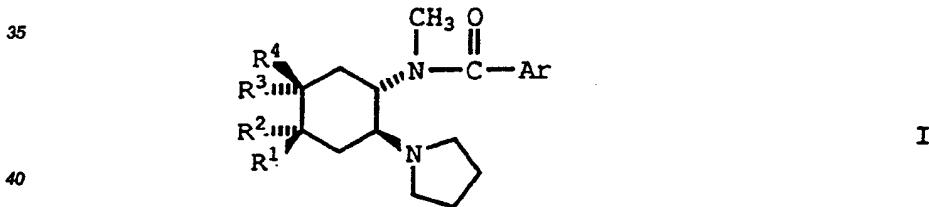
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**Description****BACKGROUND OF THE INVENTION**

- 5      The search for strong analgesics which also possess minimal potential for dependency has been among the highest priority efforts in pharmacological research. These research efforts have, to a great extent, involved chemical modifications of the opiate structure and the discovery of chemically novel compounds which possess morphine-like activity.
- 10     The concept of multiple opioid receptors has been supported by studies with nalorphine and a series of benzomorphans which display unusual pharmacological properties dissimilar from morphine, yet blocked by the opioid antagonists. [See, for example, W. R. Martin, et al., *J. Pharmacol. Exp. Ther.*, 197:517-531 (1976)].
- 15     The existence of multiple types of opioid receptors is of importance because it suggests the possibility of separating the desirable analgesic and psychotherapeutic effects of a drug compound from the undesirable abuse potential or habituating effect.
- 20     United States Patent 4,145,435 describes certain 2-amino-cycloaliphatic amide compounds as analgesics. In particular, trans-3,4-dichloro-N-methyl-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide has been reported to possess selective kappa opioid agonist activity, and therefore to possess analgesic activity without attendant dependence liability. [See P. V. Vonvoigtlander, et al., *J. Pharmacol. Exp. Ther.*, 224:7-12 (1983)].
- 25     Recently, the diuretic effect of various opioid agonists and antagonists has been studied, and it has been shown that kappa agonists tend to increase urination, while mu agonists decreased urination. [See J. D. Leander, *J. Pharmacol. Exp. Ther.*, 227:35-41 (1983)]. These findings suggest that opioid agonists and antagonists also possess potential as diuretics.
- 30     United States Patent 4,656,182 describes certain *trans*-1,2-diaminocyclohexyl amides useful as analgesics, diuretics, and psychotherapeutics.
- 35     United States Patent 4,463,013 discloses certain oxygen substituted amino-cyclohexyl-benzeneacetamides as diuretics.
- 40     United States Patent 4,438,130 discloses certain monooxa-, thiaspiro-cyclic-benzeneacetamide and benzamide compounds useful as analgesics.

**30 SUMMARY OF THE INVENTION**

One aspect of the present invention is a compound of formula

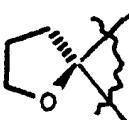


and the pharmaceutically acceptable acid addition salt thereof wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and Ar are as defined below.

45     Preferred compounds of the present invention are those of formula I wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are hydrogen.

Other preferred compounds of the present invention are those of formula I wherein one of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> is -OCH<sub>3</sub> or wherein R<sup>1</sup> and R<sup>4</sup> are both -OCH<sub>3</sub>.

50     Still other preferred compounds of the present invention are those of formula I wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form

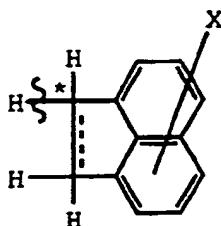


and R<sup>3</sup> and R<sup>4</sup> are both hydrogen.

Another aspect of the present invention is a compound of formula I wherein Ar is

5

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Ia

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wherein X is hydrogen.. The asterisk indicates a chiral center, both enantiomers (isomers I and II) and the racemates are preferred.

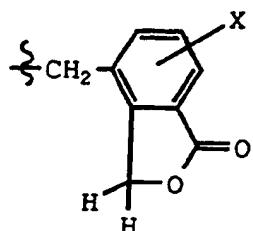
The dotted line in Ia indicates that the C<sub>1</sub>-C<sub>8</sub> bond may be unsaturated or saturated.

Another aspect of the present invention is a compound of formula I wherein Ar is

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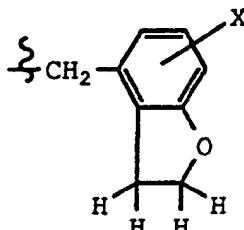
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Ic

or



Id

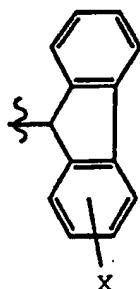
wherein X is hydrogen.

35

Another aspect of the instant invention is a compound of formula I wherein Ar is

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Ie

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wherein X is hydrogen.

Especially preferred compounds of the present invention are:

1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1 $\alpha$ ,2 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ) forms),

1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of (1 $\alpha$ ,2 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ) forms),

N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ) forms),

N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of ( $1\alpha,2\beta,4\beta,5\beta$ ) and ( $1\beta,2\alpha,4\alpha,5\alpha$ ) forms),

1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylene carboxamide, monohydrochloride (isomer I, ( $5\alpha,7\alpha,8\beta$ ) form), and

1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylene carboxamide, monohydrochloride (isomer II, ( $5\alpha,7\alpha,8\beta$ ) form).

When Isomer I and Isomer II mean the two enantiomers of the 1-acenaphthene carboxylic acid.

Another aspect of the present invention is a pharmaceutical composition useful as an analgesic, diuretic, antiinflammatory, neuroprotection or psychotherapeutic agent which comprises a therapeutically effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Yet another aspect of the present invention is the use of a compound of formula I for the preparation of a pharmaceutical useful in alleviating pain in a mammal.

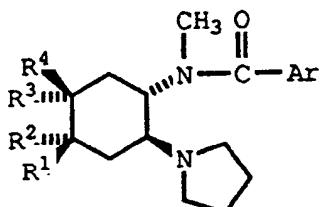
Still another aspect of the present invention is a process for the preparation of a compound of formula I described below.

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## DETAILED DESCRIPTION

The present invention is a novel series of 1,2-cyclohexylaminoaryl amides of formula I

20



30

I

and the pharmaceutically acceptable acid addition salts thereof wherein Ar, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are as described above.

The compounds of the present invention include solvates, hydrates, and pharmaceutically acceptable acid addition salts of the basic compounds of formula I above.

The term alkyl is a group of from one to six carbon atoms unless otherwise specified. This includes straight or branched groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, and the like.

By virtue of the basic nitrogen on the cyclohexane moiety, pharmaceutically acceptable salts of compounds of the present invention may be prepared by reaction with appropriate acids. Suitable acids for the formation of pharmaceutically acceptable salts of the compounds of this invention form a class well known to practitioners of the pharmaceutical formulation arts (cf. S. M. Berge, et al., "Pharmaceutical Salts" in *J. Pharm. Sci.*, 66: 1-19 (1977)), and include such acids as hydrochloric, hydrobromic, hydriodic, sulfuric, nitric, phosphoric, acetic, benzoic, citric, maleic, tartaric, succinic, gluconic, ascorbic, sulphamic, oxalic, pamoic, methanesulfonic, benzenesulfonic, ethanesulfonic, hydroxyethanesulfonic, and related acids and mixtures thereof.

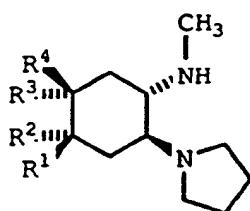
The salts are generally prepared by reacting the free base with one equivalent of the desired acid in an appropriate unreactive solvent, followed by collection of the salt by filtration or recovery upon removal of the solvent. The free base may be regenerated, if desired, by reaction of the salt with one equivalent of a base such as sodium hydroxide, sodium bicarbonate, sodium carbonate, and the like. The salts may differ from the free base form of compounds of this invention in properties such as melting point and solubility in polar solvents, but are otherwise considered equivalent for the purposes of this invention.

Compounds of the present invention contain one or more asymmetric carbon atoms and exist in various stereo- and regio-isomeric forms. The present invention contemplates all stereo- and regio-isometric forms of formula I above. The (+), (-) and ( $\pm$ ) forms are all contemplated by the instant invention.

The individual stereo compounds or enantiomers are obtained, if desired, from a mixture of different forms by known methods of resolution such as the formation of diastereomers followed by recrystallization.

Compounds of the present invention are prepared by reacting an appropriate substituted cyclohexylamine of formula I

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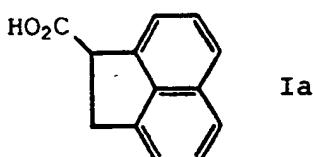


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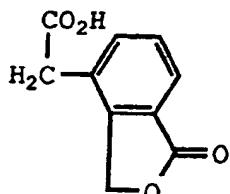
II

with an activated carboxylic acid

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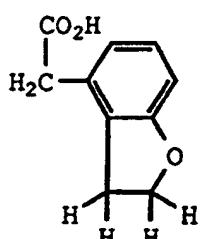
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Ic

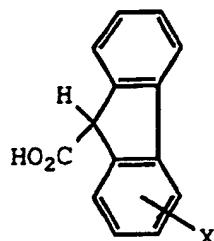
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40

Id

or



Ie

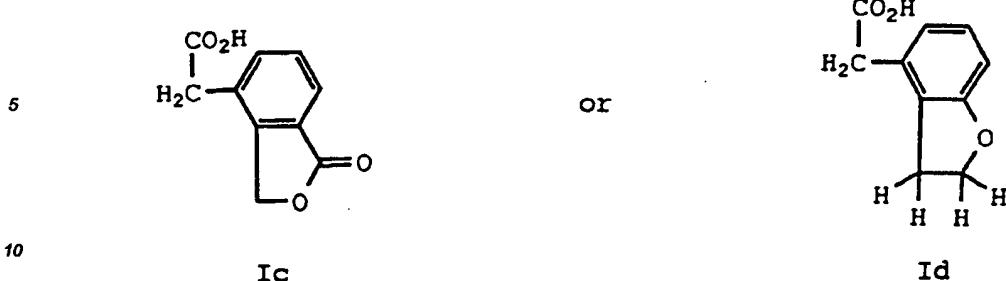
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or a reactive derivative formed from such a carboxylic acid.

First an aryl carboxylic acid is converted to the corresponding acid halide by reaction with thionyl halide. The appropriate diamine is dissolved in a suitable solvent such as dichloromethane at low temperature. Then equimolar amounts of the acid halide and the diamine are reacted to form a compound of formula I. This is recovered by precipitation from the mixed solvent. The product can be separated into diastereomers by known means.

Compounds of the present invention wherein the aryl is

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are prepared by converting the aryl carboxylic acid into the corresponding imidazole derivative by reaction with carbonyldiimidazole. The appropriate diamine is dissolved in a suitable solvent such as dichloromethane at low temperature. Then the imidazole derivative and the diamines are reacted. The reaction mixture is quenched with water and the aqueous layer is extracted with dichloromethane.

The novel compounds of the present invention have a very high kappa opioid affinity and selectivity and potency. For example, compound 1e  $K_i = 0.18$  nM with  $\mu/\kappa$  ratio of 1416 and efficacy on rat paw pressure assay better than any known compound to the inventors with MPE<sub>50</sub> 0.014 mg/kg (IV) and 0.28 mg/kg (PO).

The compounds of the present invention possess significant analgesic activity with the potential for minimum dependence liability due to their selective kappa opioid receptor properties. In addition to acting as analgesics, selective kappa opioid agonists also cause opioid receptor-mediated sedation, diuresis, and corticosteroid elevations. Accordingly, the compounds of the present invention may also be useful diuretics, anti-inflammatories and psychotherapeutic agents as well as analgesics.

25 The compounds of the present invention also have application in congestive heart failure, advanced hepatic cirrhosis, nephrotic syndrome, chronic renal failure, trauma associated with surgery, emotional and physical stress, endocrine disorders, syndrome of inappropriate antidiuretic hormone secretion and therapy with certain pharmacologic drug agents such as certain sulfonyl ureas, clofibrate, certain tricyclics such as carbamazepine, amitriptyline, thiothixene, flubenazine and thioridazine, certain antineoplastic agents, certain analgesics, and certain natriuretic diuretics.  
30

The compounds of the present invention also have neuroprotective indications. As such, they are useful in the treatment of stroke and the treatment of cerebral ischemia (P. F. Vonvoightlander in *Brain Research*, 435: 174-180 (1987)) and A. H. Tang, et al. in *Brain Research*, 403:52-57 (1987).

Representative examples of the compounds of this invention have shown activity in standard laboratory analgesic tests such as the rat paw pressure test as shown by the data appearing in Table 1 (M. B. Tyers, *Brit. J. Pharmacol.*, (1980), 69, 503-512).

Moreover, representative examples of compounds of the present invention when tested *in vitro* to determine the extent of opioid receptor were found to be selectively bound to the kappa opioid receptors with much lower binding to the mu opioid receptor sites. The benefits of this selectivity in binding to opioid receptor binding sites has been discussed above and is also described in M. B. Tyers, Br. J. Pharmacol., 69:503-512 (1980).

Measurement of the kappa opioid receptor binding activity of compounds of the present invention was made by the following method. Guinea pig brain homogenates were prepared fresh daily utilizing the method of Gillan, et al., Br. J. Pharmacol., 70:481-490 (1980).

The binding of tritiated etorphine to brain homogenates was measured in the presence of unlabeled competitors compounds of the present invention with 200 nanomolar D-alanine-D-leucine-enkephalin (acronym DADLE) and 200 nanomolar D-ala-MePheGly-ol-enkephalin (acronym DAGO) added to saturate the delta and mu opioid receptors, respectively. The reaction was terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

Measurement of the mu and delta opioid receptor binding activity of the compounds of this invention was made by the following method. Guinea pig brain homogenates were freshly prepared daily by the method of Gillan, et al., cited above.

Homogenates were incubated for 150 minutes at 0°C with either tritiated DAGO to measure mu receptor binding activity, or with tritiated DADLE in the presence of a tenfold excess of unlabeled DAGO to measure delta opioid receptor binding. Nonspecific binding was determined in the presence of 10<sup>-6</sup> molar DAGO and 10<sup>-6</sup> molar DADLE.

Reactions were terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

The data were analyzed by the methods of Scatchard, Ann. N.Y. Acad. Sci., 51:660-672 (1949) and Hill

J. Physiol., 40:IV-VIII (1910). The inhibition of the binding of tritiated etorphine, DAGO and DADLE by cold ligands was determined from the regression of log percentage inhibition of specific binding or log concentration of cold ligand. The inhibition constant,  $K_i$ , was calculated from the equation:

$$K_i = \frac{IC_{50}}{1 + [L]/K_D}$$

where  $[L]$  is the concentration of the labeled ligand and  $K_D$  is the equilibrium dissociation constant.

The results of these tests are presented in Table 1.

10

Table 1

15	Compound Number	Opioid Binding $k_i$ nM			Rat Paw Pressure MPE <sub>50</sub> (mg/kg)	
		kappa	mu	mu/k	IV	PO
1a (isomer I)	16.3	2630	161			
1b (isomer II)	31	387	12.5			
1c (isomer I)	4.5	578	128			
20 1e (isomer I)	0.18	255	1416	0.014	0.28	
1f (isomer II)	1.2	273	227			
1d (isomer II)	10.5	307	29			
3d	9.7	4930	508	0.71		
2a	0.73	653	120	0.1		
25 3c	5.3	2870	541	0.1		

30  $k_i$  values represent the mean from concentration-response curves performed in triplicate from each of at least two separate experiments.

35 MPE<sub>50</sub> values represent the dose required to produce 50% of the maximum possible analgesic effect. They are derived from a single experiment with six animals per dose level.

35

The compounds of the present invention and/or their nontoxic, pharmaceutically acceptable acid addition salts may be administered to mammals in pharmaceutical compositions which comprise one or more compounds of this invention and/or salts thereof in combination with a pharmaceutically acceptable nontoxic carrier.

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As parenteral compositions, the compounds of this invention may be administered with conventional injectable liquid carriers such as sterile, pyrogen-free water, sterile, peroxide-free ethyl oleate, dehydrated alcohols, polypropylene glycol, and mixtures thereof.

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Suitable pharmaceutical adjuvants for the injectable solutions include stabilizing agents, solubilizing agents, buffers, and viscosity regulators. Examples of these adjuvants include ethanol, ethylenediamine tetraacetic acid (EDTA), tartrate buffers, citrate buffers, and high molecular weight polyethylene oxide viscosity regulators. These pharmaceutical formulations may be injected intramuscularly, intraperitoneally, or intravenously.

50

As solid or liquid pharmaceutical compositions, the compounds of the present invention may be administered to mammals orally in combination with conventional compatible carriers in solid or liquid form. These orally administered pharmaceutical compositions may contain conventional ingredients such as binding agents such as syrups, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone, and mixtures thereof.

The compositions may further include fillers such as lactose, mannitol, starch, calcium phosphate, sorbitol, methylcellulose, and mixtures thereof.

55

These oral compositions may also contain lubricants such as magnesium stearate, high molecular weight polymers such as polyethylene glycol, high molecular weight fatty acids such as stearic acid, silica, or agents to facilitate disintegration of the solid formulation such as starch, and wetting agents such as sodium lauryl sulfate.

The oral pharmaceutical compositions may take any convenient form such as tablets, capsules, lozenges aqueous or oily suspensions, emulsions, or even dry powders which may be reconstituted with water or other suitable liquids prior to use.

5 The solid or liquid forms may contain flavorants, sweeteners, and/or preservatives such as alkyl p-hydroxybenzoates. The liquid forms may further contain suspending agents such as sorbitol, glucose, or other sugar syrups, methyl-, hydroxymethyl-, or carboxymethylcellulose, and gelatin, emulsifying agents such as lecithin or sorbitol monooleate, and conventional thickening agents. The liquid compositions may be encapsulated in, for example, gelatin capsules.

10 As topically administered pharmaceutical compositions, the compounds of the present invention may be administered in the form of ointments or creams containing from about 0.1% to about 10% by weight of the active component in a pharmaceutical ointment or cream base.

15 Compounds of the present invention may be rectally administered in the form of suppositories. For preparing suppositories, for example, a low-melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active ingredient is dispersed homogenously in the melt. The mixture is then poured into convenient sized molds and allowed to cool and solidify.

20 Preferably the pharmaceutical compositions of this invention are in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate amounts of the active component. The unit dosage can be a packaged preparation with the package containing discrete quantities of the preparation. For example, the package may take the form of packaged tablets, capsules, and powders in envelopes, vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or can be the appropriate number of any of these packaged forms.

25 The quantity of active compound in a unit dosage form may be varied or adjusted from about 0.01 mg to about 350 mg according to the particular application and the potency of the active ingredient.

25 When employed systematically in therapeutic use as analgesic agents in the pharmaceutical method of this invention, the compounds are administered at doses of from about 0.0001 mg to about 2.0 mg of active compound per kilogram of body weight of the recipient.

The following examples illustrate the present invention and are not intended to be in any way limiting.

#### EXAMPLE 1

30 Preparation of 1-Acenaphthenecarboxylic Acid

35 1-Acenaphthenecarboxylic acid was prepared by the method of Julia [Bull. Chim. Soc. Fr., 1065 (1952)] or by the preferred, shorter route described below.

35 (i) 1-Tris(methylthio)methylacenaphthene

40 Acenaphthanol (35 g) was suspended in dry ether (200 ml) cooled to -5°C with stirring and phosphorous tribromide (8 ml) added dropwise over five minutes to give a clear solution. The solution was allowed to warm to room temperature and stirred for a further two hours. The solution was washed with water and the ether layer dried over NaCO<sub>3</sub>, reduced in volume at < 40°C in vacuo to 50 ml and cooled to 0°C.

45 Bright yellow crystals (of 1-bromoacenaphthene) were isolated by filtration and used, immediately, in the following step.

Tris(methylthio)methane (22 g) was dissolved in THF (100 ml) under N<sub>2</sub> at -78°C. 1.6 M BuLi in hexane solution (95 ml) was added slowly to yield a dense white precipitate. 1-Bromoacenaphthene (31.4 g) was dissolved in 20 ml of dry THF and added slowly to the above suspension to yield, after 10 minutes, a colorless solution. This was allowed to warm to room temperature, with the development of a brown color, and stirred overnight.

50 This solution was evaporated in vacuo to yield a brown oil (48 g). This material was crystallized from hexane to give orange crystals (29 g) of 1-(trismethylthio)methyl acenaphthene. m.p. 68-70°C

Found: C, 62.62; H, 5.87; S, 31.11;  
Theory: C, 62.70; H, 5.92; S, 31.62;

55 (ii) Methyl 1-acenaphthenecarboxylate

1-Tris(methylthio)methyl acenaphthene (18.4 g), Mercury (II) Chloride (68 g) and Mercury (II) Oxide (22 g) were slurried in MeOH/H<sub>2</sub>O, 12/1 (1500 ml), stirred at room temperature for 18 hours, then refluxed for two hours, and then allowed to cool.

The suspension was filtered and the cake washed with dichloromethane ( $2 \times 100$  ml). Water ( $1500$  ml) was added to the solution and the total extracted with dichloromethane ( $2 \times 1$  L). The dichloromethane solution was washed with 75% aqueous ammonium acetate ( $2 \times 500$  ml), dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to yield an orange oil (14 g). This was then purified by chromatography using hexane/ether 25/1 as eluent and Merck 15/11 silica gel as stationary phase to give a yellow liquid (10 g).

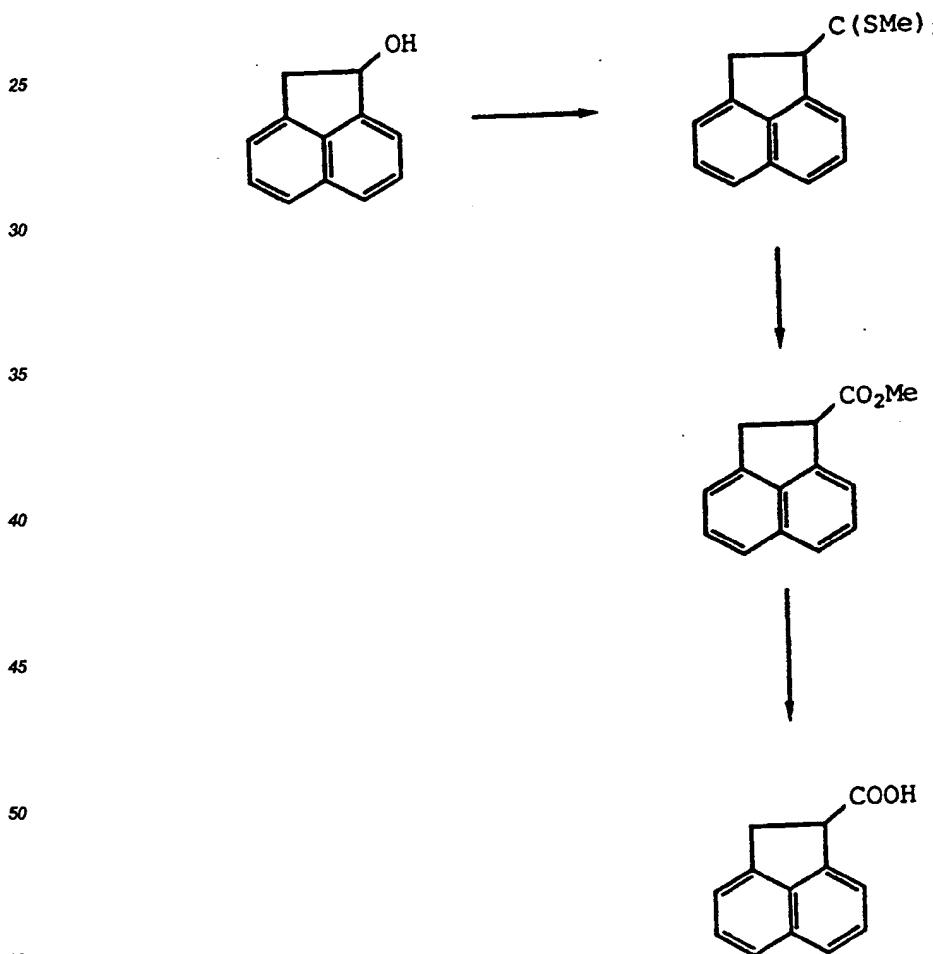
<sup>5</sup> NMR 300 MHz,  $\text{CDCl}_3$ : δ 3.67 (dd) 1H, 3.78 (s) 3H, 3.91 (dd) 1H, 4.62 (dd) 1H, 7.35 (m) 1H, 7.5 (m) 3H, 7.7 (m) 2H.

**(iii) 1-Acenaphthenecarboxylic acid**

The above ester (1.9 g) was dissolved in 5 ml THF and this solution added to 6N KOH (40 ml). The mixture was refluxed for 10 hours and allowed to cool, then acidified with 5N HCl solution and extracted with ethyl acetate ( $3 \times 50$  ml). The extracts were combined, dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to yield a gummy orange solid (1.6 g). This was recrystallized from hexane/toluene 3/1 to yield orange crystals, mp 138–145°C.

### Scheme

**Alternative Preferred Route to Acenaphthene  
Carboxylic Acid**



The acenaphthenecarboxylic acid (1.1 mmol) was stirred in neat thionyl chloride (5 ml) at reflux for one hour. The thionyl chloride was evaporated in vacuo and the resulting oil treated with 25 ml  $\text{CCl}_4$ . This mixture

was then evaporated in vacuo to yield a brown oil which was used without further purification.

The appropriate diamine of structure II (1 mmol) was dissolved in a small volume (5 ml) of dichloromethane and cooled to 0°C with stirring. The brown oil (above) was also dissolved in a similar volume of dichloromethane at room temperature and added to the acid solution dropwise. Stirring was continued for one hour at room temperature. The solution was then triturated with Et<sub>2</sub>O to yield a precipitate which was isolated by filtration.

This product was then separated into diastereoisomers (racemic pairs for Ia, Ib, Ic, Id and enantiomers for Ie and If using medium pressure silica gel chromatography (Merck 11695 15 µm silica, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 10:1 eluant). The appropriate fractions were collected, evaporated in vacuo, dissolved in dichloromethane (5 ml). This solution was then treated with ethereal HCl and evaporated in vacuo to yield a white solid, recrystallized from isopropanol.

1.a. 1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1α,2β) and (1β, 2α) forms)

15 Elemental analysis for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O·HCl·0.4H<sub>2</sub>O requires:

Calcd: C, 71.00; H, 7.89; N, 6.90

Found: C, 71.01; H, 7.75; N, 6.92

NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>) δ 1 -> 2 (m) 12H, 3.20 (s) 3H, 3.30 (m) 4H, 3.48 (m) 1H, 3.65 (m) 1H, 3.78 (d of d) 1H, 4.55 (m) 1H, 5.02 (d of d) 1H, 7.4 -> 7.6 (m) 5H.

20 mp > 230°C.

IR (liquid film) 1641 cm<sup>-1</sup> NHCO; 3400 cm<sup>-1</sup> NH<sup>+</sup>

1.b. 1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of (1α,2β) and (1β and 2α) forms)

25 Elemental analysis for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O·HCl·0.15H<sub>2</sub>O requires:

Calcd: C, 71.80; H, 7.85; N, 6.98

Found: C, 71.79; H, 7.84; N, 7.02

NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>) δ 1 -> 2 (m) 12H, 3.20 (m) and 3.32 (s) integral obscured, 3.69 (m) 4H, 4.55 (m) 1H,

30 5.02 (d of d) 1H, 7.22 (d) 1H, 7.32, 1H, 7.6 (m) 4H.

mp 228-232°C.

IR (liquid film) 1641 cm<sup>-1</sup> NHCO; 3413 NH<sup>+</sup>

1.c. N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1α,2β,4β,5β) and (1β,2α,4α,5α) forms)

Elemental analysis for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>·HCl requires:

Calcd: C, 68.03; H, 7.69; N, 6.10

Found: C, 67.88; H, 7.72; N, 6.07

40 NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>) δ 1.5 -> 2.2 (m) 8H, 3.1 (m) 1H, 3.18 (s) 3H, 3.30 (m) and 3.30 (s) and 3.35 (s) Integral obscured, 3.50 (m) 1H, 3.75 (m) 3H, 4.30 (m) 1H, 5.02 (d of d) 1H, 7.22 (d) 1H, 7.55 (m) 5H.

mp 137-140°C.

IR liquid film 1637 cm<sup>-1</sup>; NHCO 3402 cm<sup>-1</sup> NH<sup>+</sup>

45 1.d. N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of (1α,2β,4β,5β) and (1β,2α,4α,5α) forms)

Elemental analysis for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>·HCl·H<sub>2</sub>O requires:

Calcd: C, 65.46; H, 7.82; N, 5.87

50 Found: C, 65.47; H, 7.82; N, 5.90

NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>) δ 1.5 -> 2.2 (m) 8H, 3.1 (m) 1H, 3.28 (s) and 3.30 (s) and 3.33 (s) and 3.50 (m) Integral obscured, 3.80 (m) 3H, 4.80 (m) 1H, 5.02 (d of d) 1H, 7.22 (d) 1H, 7.31 (d) 1H, 7.61 (m) 4H.

mp 126-133°C.

IR Liquid film 1636 cm<sup>-1</sup> NHCO; 3392 cm<sup>-1</sup> NH<sup>+</sup>

1.e. 1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylenecarboxamide, monohydrochloride (isomer I, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ) form)

Elemental analysis for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>HCl·0.5H<sub>2</sub>O requires:

- 5 Calcd: C, 69.88; H, 7.81; N, 6.03  
 Found: C, 69.84; H, 7.77; N, 5.94  
 NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>)  $\delta$  1.5 -> 2 (m) 14H, 3.18 (s) 3H, 3.25 (m) Integral obscured 3.52 (m) 1H, 3.75 (m) 5H, 4.52 (m) 1H, 5.02 (d of d) 1H, 7.25 (d) 1H, 7.55 (m) 5H.  
 mp 143-146°C.  
 10 [α]<sub>D</sub><sup>20</sup> = + 13.9°, C = 0.17, CH<sub>2</sub>Cl<sub>2</sub>  
IR Liquid film 1640 cm<sup>-1</sup>; NHCO 3392 cm<sup>-1</sup> N-H<sup>+</sup>

1.f. 1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylenecarboxamide, monohydrochloride (isomer II, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ) form)

15 Elemental analysis for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>HCl·1.3H<sub>2</sub>O requires:

- Calcd: C, 67.77; H, 7.92; N, 5.84  
 Found: C, 67.50; H, 8.17; N, 5.48  
 NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>)  $\delta$  1.5 -> 2.1 (m) 14H, 3.20 (s) and 3.4 -> 3.8 (m) Integral obscured, 4.55 (m) 1H, 5.02 (d of d) 1H, 7.21 (d) 1H, 7.32 (d) 1H, 7.55 (m) 4H.  
 mp 138-140°C.  
 [α]<sub>D</sub><sup>20</sup> = + 43.5 C = 0.54, CH<sub>2</sub>Cl<sub>2</sub>  
IR Liquid film 1641 cm<sup>-1</sup> NHCO; 3398 cm<sup>-1</sup> N-H<sup>+</sup>

25 EXAMPLE 2

The 9-fluorenyl carboxylic acid (1.1 mmol) was stirred in neat thionyl chloride at reflux for one hour. The thionyl chloride was evaporated in vacuo and the resulting oil treated with carbon tetrachloride (25 ml). This mixture was then evaporated in vacuo to yield a brown oil (not isolated).

30 The spiroether diamine (1 mmol) was dissolved in a small volume (5 ml) of dichloromethane at 0°C with stirring. The acid chloride from above was dissolved in a similar volume of dichloromethane and this solution added to the amine solution dropwise.

Stirring was continued for one hour at room temperature, after which time the solution was triturated with H<sub>2</sub>O to yield an off-white precipitate. Recrystallized from propan-2-ol to yield white solid.

2.a. (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-9H-fluorene-9-carboxamide, monohydrochloride

40 Elemental analysis for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>HCl·0.7H<sub>2</sub>O requires:

- Calcd: C, 70.06; H, 7.51; N, 5.79  
 Found: C, 70.06; H, 7.65; N, 5.84  
 NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>)  $\delta$  1.5 -> 2.1 (m) 14H, 3.1 -> 3.8 (m) + 3.32 (s) Integral obscured, 4.55 (broad m) 1H, 5.49 (s) 1H, 7.35 (m) and 790 (m) 8H.  
 mp 201-203°C.  
 45 IR (liquid film) 1641 cm<sup>-1</sup> NHCO 3401 N-H<sup>+</sup>

2.b. ( $\pm$ )-trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-9H-fluorene-9-carboxamide, monohydrochloride

50 Elemental analysis for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O·HCl 1.4H<sub>2</sub>O requires:

- Calcd: C, 68.73; H, 7.81; N, 6.41  
 Found: C, 68.73; H, 7.93; N, 6.25  
 mp 243-252° (iPrOH) (white microcrystalline solid).  
IR (neat) 3416, 1641 cm<sup>-1</sup>  
 Mass Spec: (EI) m/e 374 (M<sup>+</sup>, 5%) 151 (100%)  
 55 NMR  $\delta$  (DMSO<sub>d</sub><sub>6</sub>) 300 MHz 10.24 (1H, br, s), 7.95 (3H, m), 7.35 (5H, m), 5.45 (1H, s), 4.58 (1H, m), 3.72 (1H, m), 3.47 (3H, s), 3.35 (4H, m), 2.2-1.22 (12H).

## EXAMPLE 3

4-Isobenzofuran-1-one acetic acid (1 mmol) and carbonyldiimidazole (1.1 mmol) were stirred under reflux in THF (10 ml) for one hour. The THF was then evaporated *in vacuo* and the residual oil dissolved in a small volume of dichloromethane (25 ml).

The diamine was dissolved in a similar small volume of dichloromethane (25 ml), cooled to 0°C and the above solution added dropwise to it, with stirring. The resulting mixture was stirred at room temperature for a further two hours and then quenched with water. The aqueous layer was extracted with dichloromethane (3 x 100 ml), the extracts combined, washed with water, dried over MgSO<sub>4</sub>, and evaporated *in vacuo*.

The resulting oil was chromatographed using Merck Silica Gel Art 11695, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 10:1 on a medium pressure preparative system.

The appropriate fractions were evaporated, the residual oil dissolved in 5 ml of dichloromethane and treated with ethereal HCl to yield a crystalline white material which was recrystallized from propan-2-ol.

15 3a. ( $\pm$ )-trans-1,3-dihydro-N-methyl-1-oxo-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-isobenzofuranacetamide, mono-hydrochloride

Elemental analysis for C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>·HCl 0.3H<sub>2</sub>O requires:

Calcd: C, 63.32; H, 7.49; N, 7.03

20 Found: C, 63.33; H, 7.37; N, 7.01

NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>) δ 1.2 -> 2.0 (m) 12H, 3.05 (s) 3H, 3.55 (m) 2H, 3.74 (d) 1H, 4.20 (d) 1H, 4.55 (broad m) 1H, 5.37 (d) 1H, 5.42 (d) 1H, 7.53 (t) 1H, 7.63 (d) 1H, 7.72 (d) 1H.

mp 251-254°C.

IR (liquid film) 1645 cm<sup>-1</sup> NHCO 1745 cm<sup>-1</sup> OCO, 3362 cm<sup>-1</sup> NH<sup>+</sup>

25 3.b. ( $\pm$ )-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )-N-[4,5-dimethoxy-2-(1-pyrrolidinyl) cyclohexyl]-1,3-dihydro-N-methyl-1-oxo-4-isobenzofuranacetamide mixture of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ) forms)

Elemental analysis for C<sub>23</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>HCl requires:

30 Calcd: C, 60.99; H, 7.34; N, 6.18

Found: C, 60.75; H, 7.41; N, 6.20

NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>) δ 1.6 -> 2.0 (m) 8H, 3.05 (s) and 3.10 (m) 4H, 3.35 (m) and 3.31 (s) and 3.33 (s) 3.35 (m) Integral obscured, 3.52 (m) 1H, 3.75 (m) 2H, 3.82 (d) 1H, 4.24 (d) 1H, 4.80 (broad m) 1H, 5.38 (d) 1H, 7.52 (t) 1H, 7.62 (d) 1H, 7.71 (d) 1H.

35 mp 250-252°C.

IR (liquid film) 1646 cm<sup>-1</sup> NHCO; 1757 cm<sup>-1</sup> COO; 3419 cm<sup>-1</sup> NH<sup>+</sup>.

3.c. (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-1,3-dihydro-N-methyl-1-oxo-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-isobenzofuranacetamide monohydrochloride

40 Elemental analysis for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>·HCl·H<sub>2</sub>O requires:

Calcd: C, 61.73; H, 7.55; N, 6.00; Cl, 7.59

Found: C, 61.99; H, 7.52; N, 5.91; Cl, 7.38

NMR 300 MHz (DMSO<sub>d</sub><sub>6</sub>) δ 1.5 -> 2.0 (m) 14H, 3.05 (s) 3H, 3.2 -> 3.6 (m) Integral obscured, 3.86 (d) 1H, 4.19 (d) 1H, 4.58 (broad m) 1H, 5.35 (d) 1H, 5.43 (d) 1H, 7.55 (t) 1H, 7.66 (d) 1H, 7.75 (d) 1H.

mp 182-184°C.

IR (liquid film) 1645 cm<sup>-1</sup> NHCO; 1757 cm<sup>-1</sup> OCO; 3425 cm<sup>-1</sup> NH<sup>+</sup>

[ $\alpha$ ]<sub>D</sub><sup>20</sup> = -1.71 C = 0.5 CH<sub>2</sub>Cl<sub>2</sub>

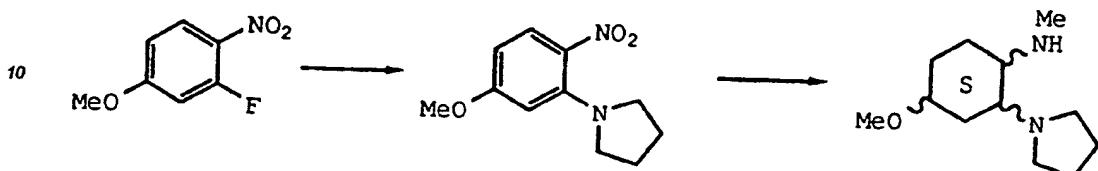
50 3.d. (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-2,3-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamide monohydrochloride

IR max: 1646 (s), 1597 cm<sup>-1</sup>

[ $\alpha$ ]<sub>D</sub> = -20°, ε = 0.64 (CH<sub>2</sub>Cl<sub>2</sub>).

## EXAMPLE 4

5 A method for preparing the diamine intermediates to 1,2-dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthylene-carboxamide monohydrochloride (isomers I and II, mixtures of (1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ ) forms), and 1,2-dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthylene-carboxamide, monohydrochloride (isomers I and II, mixtures of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ) forms).



15

3-Fluoro-4-nitroanisole

20 3-Fluoro-4-nitrophenol (Fluorochem) (10 g, 64 mmol) was dissolved in butan-2-one (60 ml) and treated with potassium carbonate 16.6 g (120 mmol) at 40°C for 10 minutes. The resulting suspension was cooled to 0°C, treated with methyl iodide (7.5 ml, 120 mmol), heated to 40°C for three hours and concentrated *in vacuo* to 20 ml. The mixture was poured into dichloromethane (35 ml), filtered and the filtrate evaporated to give 3-fluoro-4-nitroanisole, as a white solid (8.0 g, 73%). An analytically pure sample was obtained by recrystallization from aqueous ethanol (4:1); mp 47-49°C; ir 1608 cm<sup>-1</sup>.

25

3-(1-Pyrrolidinyl)-4-nitroanisole

30 3-Fluoro-4-nitroanisole (8.0 g, 47 mmol) was added over 10 minutes to pyrrolidine (25 ml) at room temperature. The resulting mixture was poured into dilute aqueous sodium hydroxide (100 ml) and extracted with dichloromethane (4 x 50 ml) to give an orange solid (7.5 g) which was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub> eluant) to give 3-(1-pyrrolidinyl)-4-nitroanisole as an orange solid (5.2 g, 50%), mp 46-48.5°; ir 1613, 1569 cm<sup>-1</sup>.

Hydrogenation of 3-pyrrolidinyl-4-nitroanisole

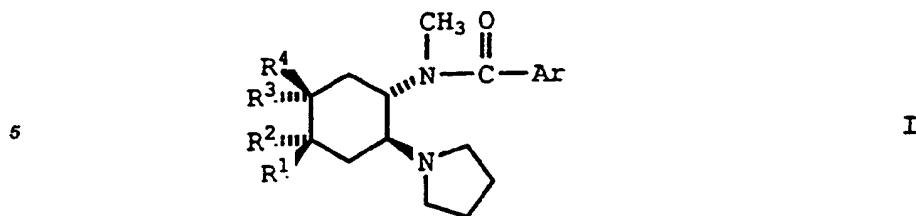
35 3-(1-Pyrrolidinyl)-4-nitroanisole (0.50 g, 2.2 mmol), 5% rhodium on alumina (0.40 g), isopropyl alcohol (75 ml) and 48 wt percent aqueous fluoroboric acid (80 mg) were treated with hydrogen at 1000 psi and 80°C for eight hours. The resulting mixture was filtered, concentrated *in vacuo*, dissolved in ethyl formate (5 ml) and triethylamine (1 ml) and heated to reflux for 50 minutes. The mixture was concentrated *in vacuo* and the residue dissolved in tetrahydrofuran (5 ml) then treated with a 1.0 M solution of lithium aluminum hydride in diethyl ether (4 ml) at 30-40°C for 12 hours. Aqueous sodium hydroxide (0.2 ml) was added and the resulting precipitate removed by filtration. The filtrate was evaporated to give an oil (0.9 g) which contains ( $\pm$ )-(1 $\alpha$ ,2 $\alpha$ ,4 $\alpha$ )-4-methoxy-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine, ( $\pm$ )-(1 $\alpha$ ,2 $\alpha$ ,4 $\beta$ )-4-methoxy-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine, ( $\pm$ )-(1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ )-4-methoxy-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine, and ( $\pm$ )-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ )-4-methoxy-N-methyl-2-(1-pyrrolidinyl)cyclohexanamine.

45

**Claims**

50 **Claims for the following Contracting States : AT, BE, CH, DE, LI, DK, FR, GB, IT, LU, NL, SE**

## 1. A compound of formula



10 and the pharmaceutically acceptable acid addition salts thereof  
 wherein  $R_1, R_2, R_3, R_4 = H$ ; or  
 wherein one of  $R_1, R_2, R_3, R_4$  may be  $= OCH_3$  when the rest are all  $H$ ; or  
 wherein  $R_1 = R_4 = OCH_3$ , and  $R_2 = R_3 = H$ ;  
 $R_1$  and  $R_2$  together form

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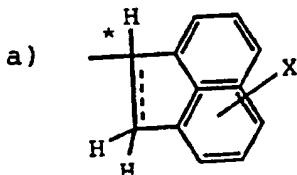
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and  $R_3, R_4$  are  $H$ ;  
 $Ar$  is

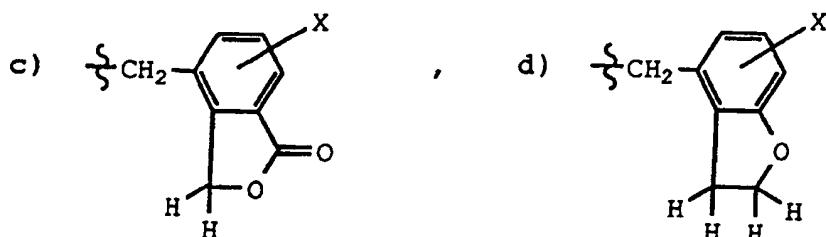
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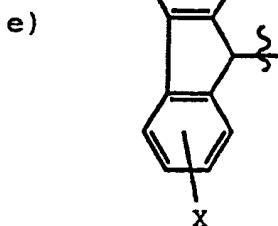


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45



wherein  $X$  is hydrogen.

55

2. A compound according to Claim 1 wherein  $R^1, R^2, R^3$ , and  $R^4$  are hydrogen.
3. A compound according to Claim 1 where one of  $R^1, R^2, R^3$ , or  $R^4$  is  $OCH_3$ .

4. A compound according to Claim 1 where R<sup>1</sup> and R<sup>4</sup> are both -OCH<sub>3</sub>.
5. A compound according to Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> taken together form

5

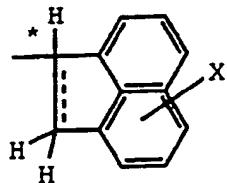


10

and R<sup>3</sup> and R<sup>4</sup> are hydrogen.

6. A compound according to Claim 1 wherein Ar is

15



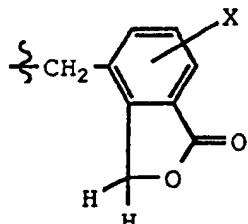
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(a)

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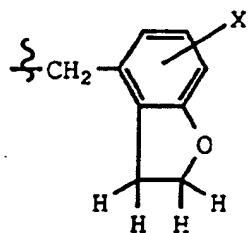
7. A compound according to Claim 1 wherein Ar is

30



35

or



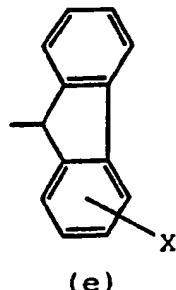
(1c)

(1d)

40

8. A compound according to Claim 1 wherein Ar is

45

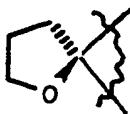


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(e)

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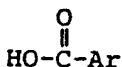
and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are hydrogen or R<sub>3</sub> and R<sub>4</sub> are hydrogen and R<sub>1</sub> and R<sub>2</sub> form



5

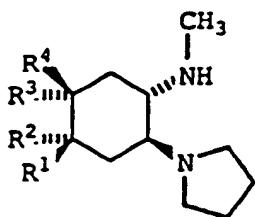
and R<sup>3</sup> and R<sup>4</sup> are hydrogen.

9. A compound according to Claim 1 selected from the group consisting of:  
 1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1 $\alpha$ ,2 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ) forms),  
 1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of (1 $\alpha$ ,2 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ) forms),  
 N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ) forms),  
 N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ) forms),  
 1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylene carboxamide, monohydrochloride (isomer I, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ) form),  
 1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylene carboxamide, monohydrochloride (isomer II, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ) form),  
 1,2-dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomers I and II, mixtures of (1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ ) forms),  
 1,2-dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomers I and II, mixtures of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ) forms).
10. A compound according to Claim 1 selected from the group consisting of:  
 (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-9H-fluorene-9-carboxamide, monohydrochloride and,  
 ( $\pm$ )-trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-9H-fluorene-9-carboxamide, monohydrochloride.
11. A compound according to Claim 1 selected from the group consisting of:  
 ( $\pm$ )-trans-1,3-dihydro-N-methyl-1-oxo-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-isobenzofuranacetamide, monohydrochloride,  
 ( $\pm$ )-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,3-dihydro-N-methyl-1-oxo-4-isobenzofuranacetamide,  
 (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-1,3-dihydro-N-methyl-1-oxo-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-isobenzofuranacetamide monohydrochloride,  
 (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-2,3-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamide monohydrochloride.
12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 to 12 in combination with a pharmaceutically acceptable carrier.
13. Use of a compound of formula I according to claims 1 to 12 for the preparation of a pharmaceutical composition useful for alleviating pain, increasing urination, treating inflammation, or treating psychotherapeutic disorders in a mammal.
14. A process for the preparation of a compound according to claims 1 - 11 characterized in that if  
 I. Ar is a) or e.)  
 a carboxylic acid of formula



is converted to the corresponding acid chloride by reaction with thionyl chloride, which is reacted with a diamine of the formula II

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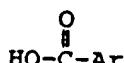
II

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wherein R¹ R² R³ and R⁴ have the above meaning and if

II. Ar is c.) or d.)

a carboxylic acid of formula



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is converted to the corresponding imidazol by reaction with carbonyldiimidazole, which is reacted with a diamine of formula II above

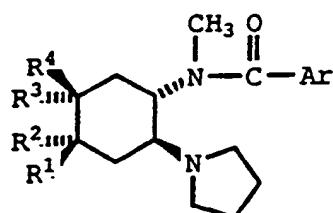
whereafter the compound of formula I if desired is converted to a pharmaceutically acceptable salt thereof.

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**Claims for the following Contracting State : ES**

1. A process for the preparation of a compound of formula I

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I

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and the pharmaceutically acceptable acid addition salts thereof

wherein R¹, R₂, R₃, R₄ = H; or

wherein one of R¹, R₂, R₃, R₄ may be = OCH₃ when the rest are all H; or

wherein R¹ = R₄ = OCH₃, and R₂ = R₃ = H;

R¹ and R₂ together form

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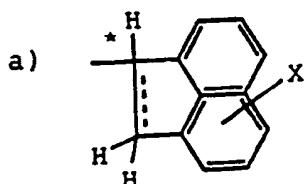


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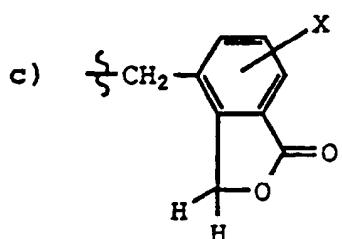
and R₃, R₄ are H;  
Ar is

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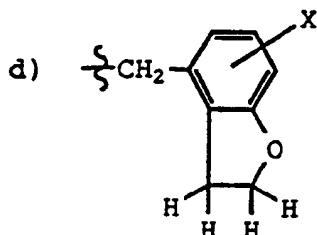
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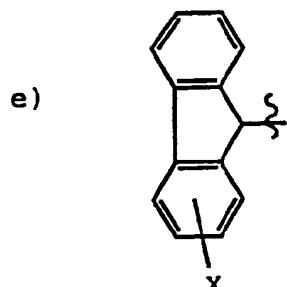
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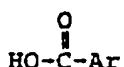
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wherein X is hydrogen.

characterized in that if

- I. Ar is a) or e.)  
a carboxylic acid of formula

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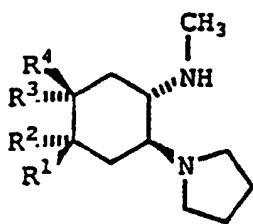


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is converted to the corresponding acid chloride by reaction with thionyl chloride, which is reacted with a diamine of the formula II

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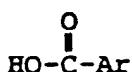
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II

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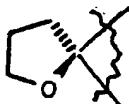
- wherein R<sup>1</sup> R<sup>2</sup> R<sup>3</sup> and R<sup>4</sup> have the above meaning and if  
II. Ar is c.) or d.)  
a carboxylic acid of formula



5       is converted to the corresponding imidazol by reaction with carbonyldiimidazole, which is reacted with a diamine of formula II above  
 whereafter the compound of formula I if desired is converted to a pharmaceutically acceptable salt thereof.

- 10      2. A process for preparing a compound according to Claim 1 wherein R<sup>1</sup> R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are hydrogen.  
          3. A process for preparing a compound according to Claim 1 where one of R<sup>1</sup> R<sup>2</sup>, R<sup>3</sup>, or R<sup>4</sup> is OCH<sub>3</sub>.  
          4. A process for preparing a compound according to Claim 1 where R<sup>1</sup> and R<sup>4</sup> are both -OCH<sub>3</sub>.  
 15      5. A process for preparing a compound according to Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> taken together form

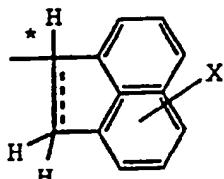
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and R<sup>3</sup> and R<sup>4</sup> are hydrogen.

- 25      6. A process for preparing a compound according to Claim 1 wherein Ar is

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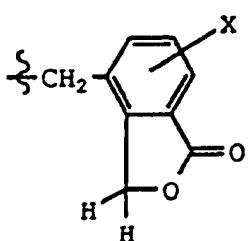
(a)

7. A process for preparing a compound according to Claim 1 wherein Ar is

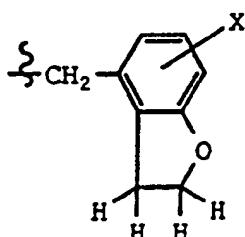
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OR



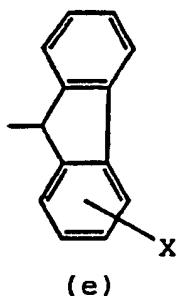
(1c)

(1d)

8. A process for preparing a compound according to Claim 1 wherein Ar is

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and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are hydrogen or R<sub>3</sub> and R<sub>4</sub> are hydrogen and R<sub>1</sub> and R<sub>2</sub> form

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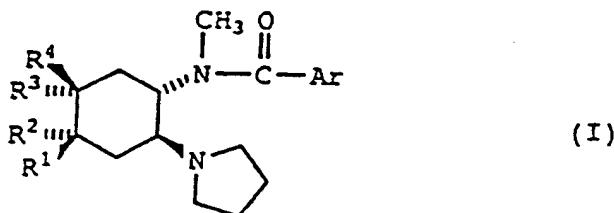
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and R<sup>3</sup> and R<sup>4</sup> are hydrogen.

9. A process for preparing a compound according to Claim 1 selected from the group consisting of:  
1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1 $\alpha$ ,2 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ) forms),  
1,2-dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of (1 $\alpha$ ,2 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ) forms),  
N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer I, mixture of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ) forms),  
N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomer II, mixture of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) and (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ) forms),  
1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylene carboxamide, monohydrochloride (isomer I, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ) form),  
1,2-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthylene carboxamide, monohydrochloride (isomer II, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ) form),  
1,2-dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomers I and II, mixtures of (1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ ) forms),  
1,2-dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthylene carboxamide, monohydrochloride (isomers I and II, mixtures of (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ) forms).
10. A process for preparing a compound according to Claim 1 selected from the group consisting of:  
(-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-9H-fluorene-9-carboxamide, monohydrochloride and,  
( $\pm$ )-trans-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-9H-fluorene-9-carboxamide, monohydrochloride.
11. A process for preparing a compound according to Claim 1 selected from the group consisting of:  
( $\pm$ )-trans-1,3-dihydro-N-methyl-1-oxo-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-isobenzofuran acetamide, monohydrochloride,  
( $\pm$ )-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )-N-[4,5-dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,3-dihydro-N-methyl-1-oxo-4-isobenzofuran acetamide,  
(-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-1,3-dihydro-N-methyl-1-oxo-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-isobenzofuran acetamide monohydrochloride,  
(-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-2,3-dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4-5]dec-8-yl]-4-benzofuran acetamide monohydrochloride.
12. Use of a compound of formula I prepared according to claims 1 to 12 for the preparation of a pharmaceutical composition useful for alleviating pain, increasing urination, treating inflammation, or treating psychotherapeutic disorders in a mammal.

**Patentansprüche****Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE**5    **1. Verbindung der Formel I**

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und die pharmazeutisch annehmbaren Säureadditionssalze dieser Verbindung,  
 worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> = H; oder  
 worin eines der Symbole R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> OCH<sub>3</sub> bedeuten kann, wenn die übrigen sämtlich für H stehen;  
 oder  
 20    worin R<sup>1</sup> = R<sup>4</sup> = OCH<sub>3</sub> und R<sup>2</sup> = R<sup>3</sup> = H;  
 R<sup>1</sup> und R<sup>2</sup> zusammen eine Gruppe

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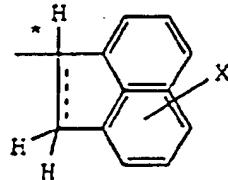


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bilden und R<sup>3</sup> und R<sup>4</sup> für H stehen; und Ar die folgenden Bedeutungen hat:  
 Ar

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a)

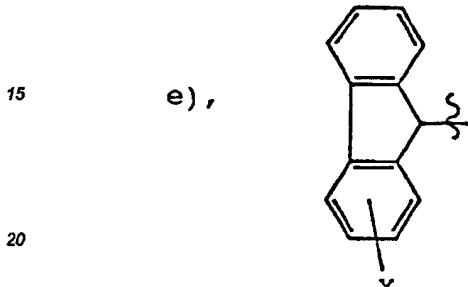
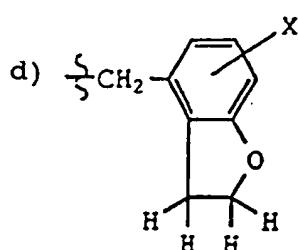
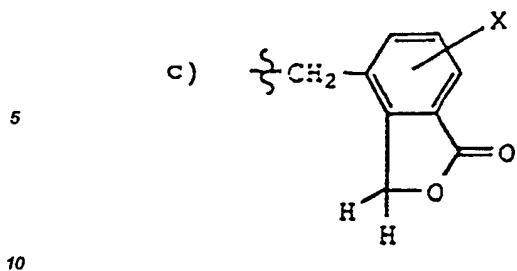


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worin X Wasserstoff bedeutet.

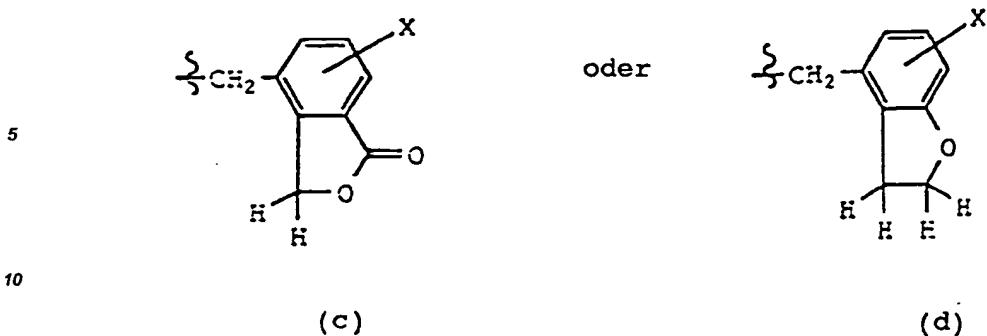
- 25            2. Verbindung nach Anspruch 1, worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten.  
 3. Verbindung nach Anspruch 1, worin eines der Symbole R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> oder R<sup>4</sup> für OCH<sub>3</sub> steht.  
 30            4. Verbindung nach Anspruch 1, worin R<sup>1</sup> und R<sup>4</sup> beide für OCH<sub>3</sub> stehen.  
 5. Verbindung nach Anspruch 1, worin R<sup>1</sup> und R<sup>2</sup> zusammen eine gruppe



- 40            bilden und R<sup>3</sup> und R<sup>4</sup> für Wasserstoff stehen.  
 6. Verbindung nach Anspruch 1, worin Ar für



- (a)
- 55            steht.  
 7. Verbindung nach Anspruch 1, worin Ar für



steht.

- 15
8. Verbindung nach Anspruch 1, worin Ar für



30

steht und R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, oder R<sup>3</sup> und R<sup>4</sup> für Wasserstoff stehen und R<sup>1</sup> und R<sup>2</sup> eine Gruppe



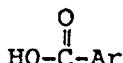
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bilden.

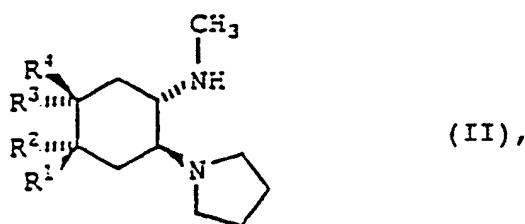
- 45
9. Verbindung nach Anspruch 1, ausgewählt aus der aus folgenden Verbindungen bestehenden Gruppe:  
1,2-Dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylencarboxamid, Monohydrochlorid  
(Isomer I, Mischung aus (1 $\alpha$ ,2 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ )-Formen);  
1,2-Dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylencarboxamid, Monohydrochlorid  
(Isomer II, Mischung aus (1 $\alpha$ ,2 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ )-Formen);  
N-[4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthenylcarboxamid, Monohy-  
drochlorid (Isomer I, Mischung aus (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )- Formen);  
N-[4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthenylcarboxamid, Monohy-  
drochlorid (Isomer II, Mischung aus (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )- Formen);  
1,2-Dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]-dec-8-yl]-1-acenaphthenylcarboxamid, Monohy-  
drochlorid (Isomer I, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-Form);  
1,2-Dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]-dec-8-yl]-1-acenaphthenylcarboxamid, Monohy-  
drochlorid (Isomer II, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-Form);  
1,2-Dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthenylcarboxamid, Mono-  
hydrochlorid (Isomere I und II, Mischungen aus (1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ )-Formen);  
1,2-Dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthenylcarboxamid, Mono-

hydrochlorid (Isomere I und II, Mischungen aus (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ )-Formen).

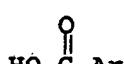
- 5        10. Verbindung nach Anspruch 1, ausgewählt aus der aus folgenden Verbindungen bestehenden Gruppe:  
           (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-9H-fluoren-9-carboxamid, Monohydrochlorid  
           und  
           ( $\pm$ )-trans-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-9H-fluoren-9-carboxamid, Monohydrochlorid.
- 10      15. Verbindung nach Anspruch 1, ausgewählt aus der aus folgenden Verbindungen bestehenden Gruppe:  
           ( $\pm$ )-trans-1,3-Dihydro-N-methyl-1-oxo-N-[2-(1-pyrrolidinyl)-cyclohexyl]-4-isobenzofuranacetamid, Monohydrochlorid;  
           ( $\pm$ )-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )-N-[4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,3-dihydro-N-methyl-1-oxo-4-isobenzofuranacetamid;  
           (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-1,3-Dihydro-N-methyl-1-oxo-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-isobenzofuranacetamid, Monohydrochlorid; und  
           (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-2,3-Dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamid, Monohydrochlorid.
- 15      20. Pharmazeutische Zubereitung, enthaltend eine therapeutisch wirksame Menge einer Verbindung nach den Ansprüchen 1 bis 11 in Kombination mit einem pharmazeutisch annehmbaren Trägerstoff.
- 20      25. 13. Verwendung einer Verbindung nach den Ansprüchen 1 bis 11 zur Herstellung einer pharmazeutischen Zubereitung, die zur Linderung von Schmerzen, Verstärkung der Blasenentleerung, Behandlung von Entzündungen oder zur Behandlung psychotherapeutischer Störungen bei Säugetieren verwendbar ist.
- 25      14. Verfahren zur Herstellung einer Verbindung nach den Ansprüchen 1 bis 11, dadurch gekennzeichnet, dass man
- I. wenn Ar für (a) oder (e) steht, eine Carbonsäure der Formel



35        durch Umsetzen, mit Thionylchlorid in das entsprechende Säurechlorid überführt, welches man mit einem Diamin der Formel II



worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> die oben angegebenen Bedeutungen haben, umsetzt; und  
 II. wenn Ar für (c) oder (d) steht, eine Carbonsäure der Formel



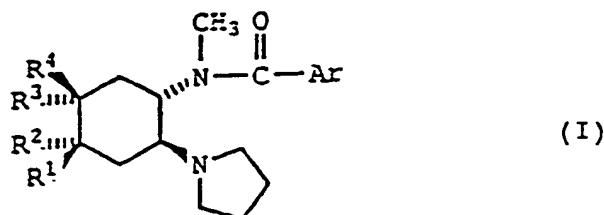
55        durch Umsetzung mit einem Carbonyldiimidazol in das entsprechende Imidazol überführt, welches man mit einem Diamin der obenstehenden Formel II umsetzt,  
           worauf man die erhaltene Verbindung der Formel I, sofern erwünscht, in eines ihrer pharmazeutisch annehmbaren Säureadditionssalze überführt.

## Patentansprüche für folgenden Vertragsstaat : ES

## 1. Verfahren zur Herstellung einer Verbindung der Formel I

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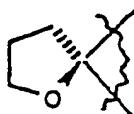
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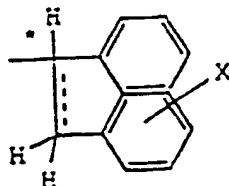
und der pharmazeutisch annehmbarer Säureadditionssalze dieser Verbindung,  
 worin  $R^1, R^2, R^3, R^4 = H$ ; oder  
 worin eines der Symbole  $R^1, R^2, R^3, R^4 = OCH_3$  bedeuten kann, wenn die übrigen sämtlich für  $H$  stehen;  
 oder  
 worin  $R^1 = R^4 = OCH_3$  und  $R^2 = R^3 = H$ ;  
 $R^1$  und  $R^2$  zusammen eine Gruppe



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bilden und  $R^3$  und  $R^4$  für  $H$  stehen; und Ar die folgenden Bedeutungen hat:  
 Ar

a)



35

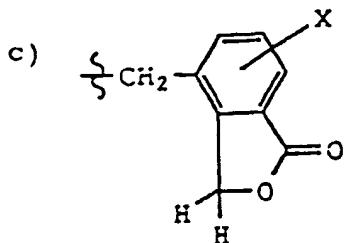
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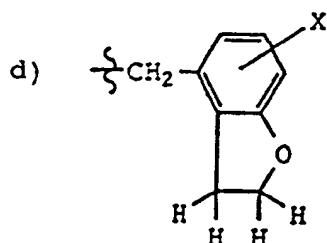
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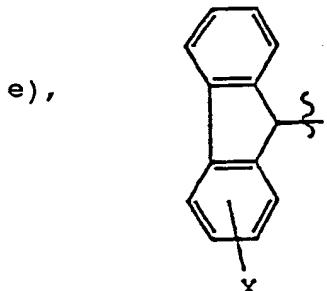
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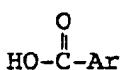
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worin X Wasserstoff bedeutet, dadurch gekennzeichnet, dass man  
I. wenn Ar für (a) oder (e) steht, eine Carbonsäure der Formel

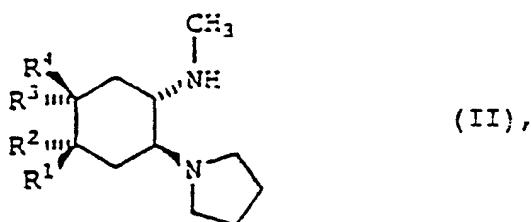


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durch Umsetzung mit Thionylchlorid in das entsprechende Säurechlorid überführt, welches man mit  
einem Diamin der Formel II

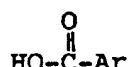
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worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> die oben angegebenen Bedeutungen haben, umsetzt; und  
II. wenn Ar für (c) oder (d) steht, eine Carbonsäure der Formel



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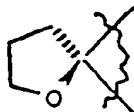
durch Umsetzung mit einem Carbonyldiimidazol in das entsprechende Imidazol überführt, welches  
man mit einem Diamin der obenstehenden Formel II umsetzt,  
worauf man die erhaltene Verbindung der Formel I, sofern erwünscht, in eines ihrer pharmazeutisch an-  
nehmbaren Säureadditionssalze überführt.

55

2. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> Wasserstoff be-  
deuten.

3. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin eines der Symbole R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> oder R<sup>4</sup> für OCH<sub>3</sub> steht.
4. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin R<sup>1</sup> und R<sup>4</sup> beide für OCH<sub>3</sub> stehen.
5. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin R<sup>1</sup> und R<sup>2</sup> zusammen eine Gruppe

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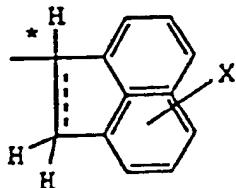


bilden und R<sup>3</sup> und R<sup>4</sup> für Wasserstoff stehen.

15

6. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin Ar für

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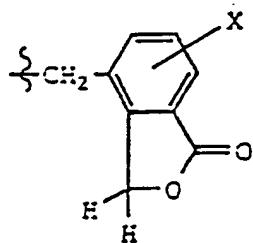
(a)

steht.

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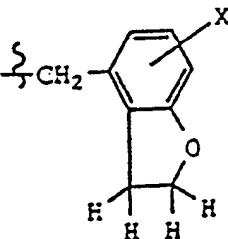
7. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin Ar für

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oder

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(c)

(d)

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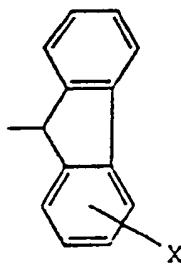
steht.

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8. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin Ar für

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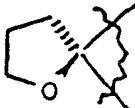
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(e)

steht und R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, oder R<sup>3</sup> und R<sup>4</sup> für Wasserstoff stehen und R<sup>1</sup> und R<sup>2</sup> eine Gruppe

15

20



bilden.

25 9. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, ausgewählt aus der aus folgenden Verbindungen bestehenden Gruppe:

1,2-Dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylencarboxamid, Monohydrochlorid (Isomer I, Mischung aus (1 $\alpha$ ,2 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ )-Formen);

1,2-Dihydro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acenaphthylencarboxamid, Monohydrochlorid (Isomer II, Mischung aus (1 $\alpha$ ,2 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ )-Formen);

N-[4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthenylcarboxamid, Monohydrochlorid (Isomer I, Mischung aus (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )-Formen);

N-[4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-methyl-1-acenaphthenylcarboxamid, Monohydrochlorid (Isomer II, Mischung aus (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )- und (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )-Formen);

1,2-Dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthenylcarboxamid, Monohydrochlorid (Isomer I, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-Form);

1,2-Dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-1-acenaphthenylcarboxamid, Monohydrochlorid (Isomer II, (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-Form);

1,2-Dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthenylcarboxamid, Monohydrochlorid (Isomere I und II, Mischungen aus (1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ )-Formen);

1,2-Dihydro-N-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-1-acenaphthenylcarboxamid, Monohydrochlorid (Isomere I und II, Mischungen aus (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ )-Formen).

45 10. Verbindung nach Anspruch 1, ausgewählt aus der aus folgenden Verbindungen bestehenden Gruppe:

(-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-9H-fluoren-9-carboxamid, Monohydrochlorid

und

( $\pm$ )-trans-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-9H-fluoren-9-carboxamid, Monohydrochlorid.

50 11. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, ausgewählt aus der aus folgenden Verbindungen bestehenden Gruppe:

( $\pm$ )-trans-1,3-Dihydro-N-methyl-1-oxo-N-[2-(1-pyrrolidinyl)-cyclohexyl]-4-isobenzofuranacetamid, Monohydrochlorid;

( $\pm$ )-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )-N-[4,5-Dimethoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,3-dihydro-N-methyl-1-oxo-4-isobenzofuranacetamid;

(-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-1,3-Dihydro-N-methyl-1-oxo-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-isobenzofuranacetamid, Monohydrochlorid; und

(-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-2,3-Dihydro-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamid,

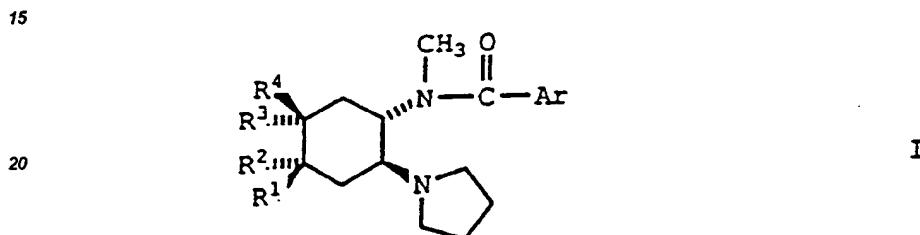
Monohydrochlorid.

12. Verwendung einer nach den Ansprüchen 1 bis 11 hergestellten Verbindung zur Herstellung einer pharmazeutischen Zubereitung, die zur Linderung von Schmerzen, Verstärkung der Blasenentleerung, Behandlung von Entzündungen oder zur Behandlung psychotherapeutischer Störungen bei Säugetieren verwendbar ist.

**Revendications**

10 Revendications pour les Etats contractants suivants : AT, BE, CH, DE, LI, DK, FR, GB, IT, LU, NL, SE

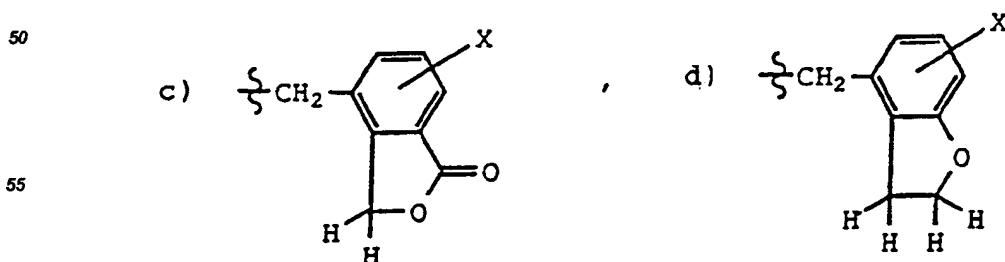
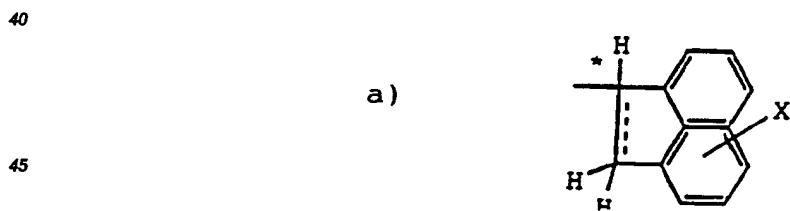
15 1. Composé de la formule



20 et ses sels d'addition d'acides pharmaceutiquement acceptables,  
dans laquelle R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> = H, ou  
dans laquelle l'un des symboles R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> peut représenter un groupe -OCH<sub>3</sub> lorsque tous les autres symboles sont H, ou  
dans laquelle R<sub>1</sub> = R<sub>4</sub> = OCH<sub>3</sub> et R<sub>2</sub> = R<sub>3</sub> = H,  
R<sub>1</sub> et R<sub>2</sub> forment ensemble



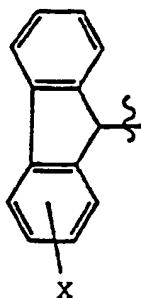
et R<sub>3</sub>, R<sub>4</sub> sont H,  
Ar est



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e )

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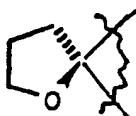


où X représente un atome d'hydrogène.

- 15 2. Composé suivant la revendication 1, caractérisé en ce que R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> représentent des atomes d'hydrogène.
3. Composé suivant la revendication 1, caractérisé en ce que l'un des symboles R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, et R<sup>4</sup> représente un groupe -OCH<sub>3</sub>.
- 20 4. Composé suivant la revendication 1, caractérisé en ce que R<sup>1</sup> et R<sup>2</sup> représentent tous deux des groupes -OCH<sub>3</sub>.
5. Composé suivant la revendication 1, caractérisé en ce que R<sup>1</sup> et R<sup>2</sup>, considérés ensemble, forment un  
25 groupement

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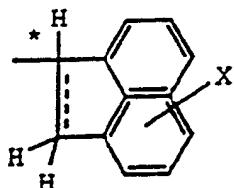


et R<sup>3</sup> et R<sup>4</sup> sont des atomes d'hydrogène.

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6. Composé suivant la revendication 1, caractérisé en ce que Ar représente le groupe

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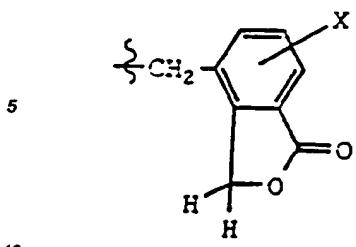
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( a )

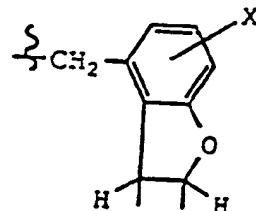
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7. Composé suivant la revendication 1, caractérisé en ce que Ar représente le groupe

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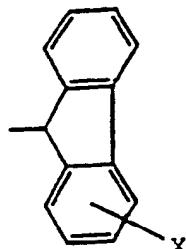
(1c)



(1d)

- 15 8. Composé suivant la revendication 1, caractérisé en ce que Ar représente le radical

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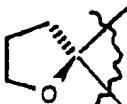


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(e)

et les symboles R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> et R<sub>4</sub> représentent des atomes d'hydrogène, ou bien R<sub>3</sub> et R<sub>4</sub> représentent des atomes d'hydrogène et R<sub>1</sub> et R<sub>2</sub> et forment un groupement

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et R<sub>3</sub> et R<sub>4</sub> représentent des atomes d'hydrogène.

9. Composés suivant la revendication 1, choisi dans le groupe formé par les substances suivantes :

40 1,2-dihydro-N-méthyl-N[2-(1-pyrrolidinyl)cyclohexyl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère I, mélange des formes (1 $\alpha$ ,2 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ )),

45 1,2-dihydro-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère II, mélange des formes (1 $\alpha$ ,2 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ )),

N-[4,5-diméthoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomère I, mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )),

45 N-[4,5-diméthoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomère II, mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )),

1,2-dihydro-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère I, forme (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )),

50 1,2-dihydro-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère II, forme (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )),

1,2-dihydro-N-[4-méthoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomères I et II, mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ )),

1,2-dihydro-N-[4-méthoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomères I et II) mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ).

- 55 10. Composé suivant la revendication 1, choisi dans le groupe formé par les substances suivantes :

(-)-5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ -N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-9H-fluorène-9-carboxamide, mo-

### **nochlorhydrate**

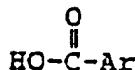
( $\pm$ )-trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-9H-fluorène-9-carboxamide, monochlorhydrate.

- 5 11. Composé suivant la revendication 1 choisi dans le groupe formé par les substances suivantes :  
 $(\pm)$ -trans-1,3-dihydro-N-méthyl-1-oxo-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-isobenzofuranacétamide, monochlorhydrate,  
 $(\pm)$ -(1 $\alpha$ ,2B,4B,5B)-N-[4,5-diméthoxy-2-(1-pyrrolidinyl)cyclohexyl]1,3-dihydro-N-méthyl-1-oxo-4-isobenzofuranacétamide,  
10 (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-1,3-dihydro-N-méthyl-1-oxo-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-4-isobenzofuranacétamide monochlorhydrate,  
(-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-2,3-dihydro-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-4-benzofuranacétamide monochlorhydrate.

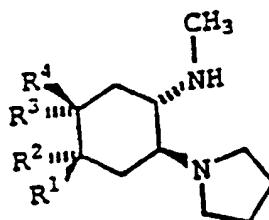
15 12. Composition pharmaceutique comprenant une proportion thérapeutiquement efficace d'un composé suivant l'une quelconque des revendications 1 à 12, en combinaison avec un véhicule ou excipient pharmaceutiquement acceptable.

13. Utilisation d'un composé de la formule I suivant les revendications 1 à 12 en vue de la préparation d'une composition pharmaceutique convenant au soulagement de la douleur, à l'augmentation de l'excrétion d'urine, au traitement des inflammations, ou au traitement de troubles psychothérapeutiques, chez un mammifère.

20 14. Procédé de préparation d'un composé suivant l'une quelconque des revendications 1 à 11, caractérisé en ce que, si  
I. Ar est a) ou e),  
on convertit un acide carboxylique de la formule



en le chlorure d'acide correspondant par réaction avec le chlorure de thionyle, que l'on fait réagir avec une diamine de la formule

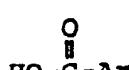


II

dans laquelle R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> possèdent les significations qui leur ont été précédemment attribuées et si

#### II. Ar est c) ou d)

on convertit un acide carboxylique de la formule

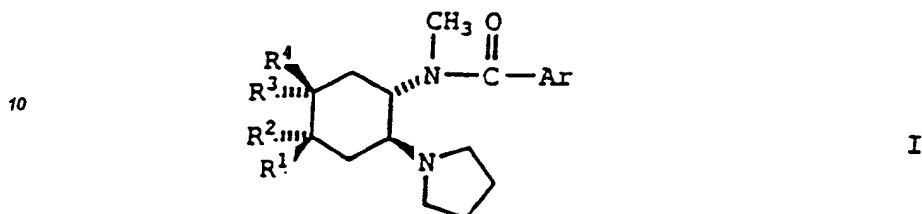


en l'imidazole correspondant par réaction avec le carbonyldiimidazole, que l'on fait réagir avec une diamine de la formule II susmentionnée, puis, si on le souhaite, on convertit le composé de la formule I en un sel pharmaceutiquement acceptable de

celui-ci.

**Revendications pour l'Etat contractant suivant : ES**

5 1. Procédé de préparation d'un composé de la formule I

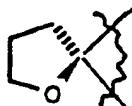


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et ses sels d'addition d'acides pharmaceutiquement acceptables,  
 dans laquelle R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> = H, ou  
 dans laquelle l'un des symboles R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> peut représenter un groupe -OCH<sub>3</sub> lorsque tous les autres symboles sont H, ou  
 20 dans laquelle R<sub>1</sub> = R<sub>4</sub> = OCH<sub>3</sub> et R<sub>2</sub> = R<sub>3</sub> = H,  
 R<sub>1</sub> et R<sub>2</sub> forment ensemble

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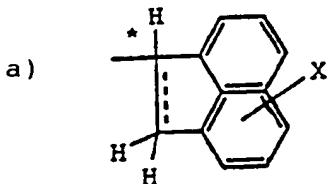
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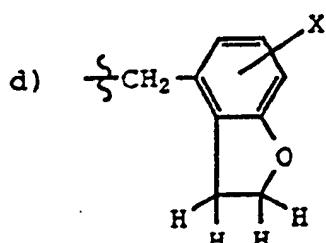
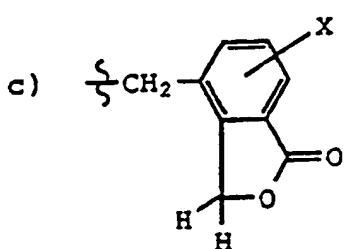
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et R<sub>3</sub>, R<sub>4</sub> sont H,  
 Ar est

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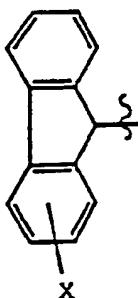
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e)



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où X représente un atome d'hydrogène,  
caractérisé en ce que, si

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I. Ar est a) ou e),  
on convertit un acide carboxylique de la formule

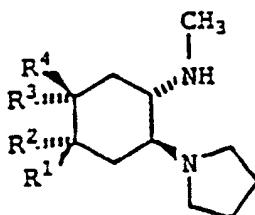
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en le chlorure d'acide correspondant par réaction avec le chlorure de thionyle, que l'on fait réagir avec  
une diamine de la formule

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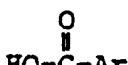
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II

dans laquelle R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> possèdent les significations qui leur ont été précédemment attribuées  
et, si

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II. Ar est c) ou d),  
on convertit un acide carboxylique de la formule



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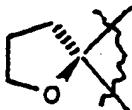
en l'imidazole correspondant par réaction avec le carbonyldiimidazole, que l'on fait réagir avec une dia-  
mine de la formule II susmentionnée, puis,  
si on le souhaite, on convertit le composé de la formule I en un sel pharmaceutiquement acceptable de  
celui-ci.

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2. Procédé de préparation d'un composé suivant la revendication 1, caractérisé en ce que R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup>  
représentent des atomes d'hydrogène.
3. Procédé de préparation d'un composé suivant les revendication 1, caractérisé en ce que l'un des symboles  
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> représente un groupe -OCH<sub>3</sub>.
4. Procédé de préparation d'un composé suivant la revendication 1, caractérisé en ce que R<sup>1</sup> et R<sup>4</sup> repré-  
sentent tous deux des groupes -OCH<sub>3</sub>.

5. Procédé de préparation d'un composé suivant la revendication 1 caractérisé en ce que R<sup>1</sup> et R<sup>2</sup> considérés ensemble, forment un groupement

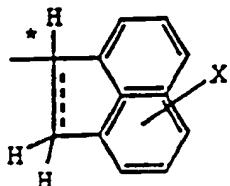
5



10 et R<sup>3</sup> et R<sup>4</sup> représentent des atomes d'hydrogène.

6. Procédé de préparation d'un composé suivant la revendication 1, caractérisé en ce que Ar représente un radical

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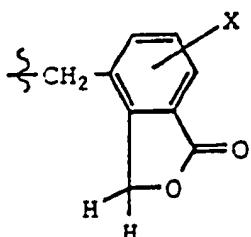
20

(a)

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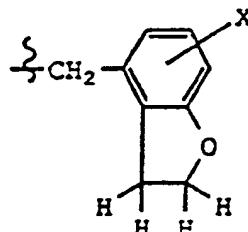
7. Procédé de préparation d'un composé suivant la revendication 1, caractérisé en ce que Ar représente un radical

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ou



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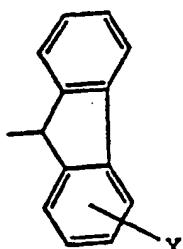
(1c)

(1d)

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8. Procédé de préparation d'un composé suivant la revendication 1, caractérisé en ce que Ar représente le radical

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(e)

et les symboles R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> et R<sub>4</sub> représentent des atomes d'hydrogène, ou bien R<sub>3</sub> et R<sub>4</sub> représentent des atomes d'hydrogène et R<sub>1</sub> et R<sub>2</sub> forment un groupement

et R<sub>3</sub> et R<sub>4</sub> représentent des atomes d'hydrogène.

9. Procédé de préparation d'un composé suivant la revendication, choisi dans le groupe formé par les substances suivantes :
- 5 1,2-dihydro-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère I, mélange des formes (1 $\alpha$ ,2 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ )),
- 10 1,2-dihydro-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère II, mélange des formes (1 $\alpha$ ,2 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ )),
- 15 N-[4,5-diméthoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomère I, mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )),
- 20 N-[4,5-diméthoxy-2-(1-pyrrolidinyl)cyclohexyl]-1,2-dihydro-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomère II, mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ ) et (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ )),
- 25 1,2-dihydro-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère I, forme (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )),
- 1,2-dihydro-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-1-acénaphthylène carboxamide, monochlorhydrate (isomère II, forme (5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )),
- 30 1,2-dihydro-N-[4-méthoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomères I et II, mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\alpha$ )),
- 35 1,2-dihydro-N-[4-méthoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-méthyl-1-acénaphthylène carboxamide, monochlorhydrate (isomères I et II) mélange des formes (1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ).
10. Procédé de préparation d'un composé suivant la revendication 1, choisi dans le groupe formé par les substances suivantes :
- 25 (-)-5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ -N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-9H-fluorène-9-carboxamide, monochlorhydrate et
- (±)-trans-N-méthyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-9H-fluorène-9-carboxamide, monochlorhydrate.
11. Procédé de préparation d'un composé suivant la revendication 1 choisi dans le groupe formé par les substances suivantes :
- 30 (±)-trans-1,3-dihydro-N-méthyl-1-oxo-N-[2-(1-pyrrolidinyl)cyclohexyl]-4-isobenzofuranacétamide, monochlorhydrate,
- (±)-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\beta$ )-N-(4,5-diméthoxy-2-(1-pyrrolidinyl)cyclohexyl)-1,3-dihydro-N-méthyl-1-oxo-4-isobenzofuranacétamide,
- 35 (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-1,3-dihydro-N-méthyl-1-oxo-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-4-isobenzofuranacétamide monochlorhydrate,
- (-)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-2,3-dihydro-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-4-benzofuranacétamide monochlorhydrate.
12. Composition pharmaceutique comprenant une proportion thérapeutiquement efficace d'un composé suivant l'une quelconque des revendications 1 à 12, en combinaison avec un véhicule ou excipient pharmaceutiquement acceptable.

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